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(54) Title: COMPOSITIONS COMPRISING LYCOPENE FOR THE TREATMENT AND PREVENTION OF ANGIOGENESIS ASSOCIATED PATHOLOGIES

(57) Abstract: The invention is concerned with the use of lycopene, optionally in combination with vitamin E and/or C or other biologically active ingredients as disclosed in the specification, in the manufacture of a composition for the primary and secondary prevention of angiogenesis-associated pathologies and coadjuvant treatment thereof, as well as with particular novel formulations comprising lycopene.

COMPOSITIONS COMPRISING LYCOPENE FOR THE TREATMENT AND PREVENTION OF ANGIOGENESIS ASSOCIATED PATHOLOGIES

The present invention relates to the use of lycopene in the prevention and coadjuvant treatment of angiogenesis-associated pathologies. More specifically, the present invention relates to the use of lycopene in the primary prevention (i.e., the prophylactic supplementation of healthy subjects) of the onset of angiogenesis-associated pathologies, in the coadjuvant treatment (i.e. the supplementation accompanying a running therapy of angiogenesis-associated pathologies) and in the secondary prevention (i.e., the supplementation after a successful therapy for the prevention of relapse) of angiogenesis-associated pathologies.

Angiogenesis, the process of new capillary formation from the preexisting vasculature, is required for successful tumor growth and metastasis. Furthermore, increased neovascularisation is part of the pathology of several non-cancerous diseases, e.g. in chronic inflammations and several eye diseases.

When a primary tumor first arises, proliferation of cancer cells may be balanced by apoptosis, and the tumor may remain undetectable for years until neovascularization appears. Though the relative sudden onset of neovascularization in primary tumors, described as angiogenic switch from avascular to vascular phenotypes, is a discrete event distinct from tumor initiation, unrestricted growth of solid tumors is limited by angiogenesis, as in the absence of access to an adequate vasculature, tumor cells become necrotic and/or apoptotic. For several carcinomas, an elevated serum VEGF level, the major inducer of angiogenesis, is reported, e.g. for epithelial ovarian neoplasms, esophageal squamous cell carcinoma, head and neck carcinoma, lung carcinoma, non-Hodgkin lymphoma, ovarian carcinoma, prostate carcinoma, renal cell carcinoma, and urothelial carcinoma. Furthermore, angiogenesis and the vascular density of tumors have been shown to be associated with tumor metastasis. Several studies reveal that the higher the microvessel count is in areas of highest vessel density, the lower is the rate of overall survival of the tumor patients, see Weidner N, Semple JP, Welch WR, Folkman J. Tumor

angiogenesis and metastasis-correlation in invasive breast carcinoma. N Engl J Med (1991) 324:1-8.

Beside cancer, other diseases are also associated with increased neovascularization. In the first acute phase of inflammation, functional changes in the vasculature, such as dilatation, increase in permeability and endothelial activation occur. In the second subacute phase, capillaries and venules remodel with extensive endothelial mitotic activity. Upon chronic stimulation, both increases in capillary density and vascular dilatation can be observed, although these responses can differ significantly between strains of mice and possibly between species. In many chronic inflammatory diseases, e.g. in rheumatoid arthritis or in psoriasis, neovascularization can be identified in the inflamed lesions. These observed pathology accompanying neovascularizations are in line with reports of elevated serum VEGF levels, the major inducer of angiogenesis, in several inflammatory diseases, e.g. inflammatory bowel disease comprising ulcerative colitis and Crohn's disease, inflammatory arthritis (rheumatoid arthritis, self-limiting arthritis and psoriatic arthritis) and osteoarthritis.

Diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity belong to a group of ischemic retinal disorders which are associated with intraocular neovascularization. In neovascular retinopathies, such as proliferative diabetic retinopathy, there is initially extensive active proliferation of new vessels. It has been shown that increased angiogenesis is a central element in these eye pathologies.

Furthermore, neovascularization is a principal cause of visual loss also in the wet form of age-related macular degeneration (AMD), the overall leading cause of blindness.

According to the present invention, it has been found that angiogenesis can be suppressed or inhibited by the administration of lycopene.

The present invention, therefore, is concerned with the use of lycopene in the manufacture of a composition for the primary and secondary prevention of angiogenesis-associated pathologies and coadjuvant treatment thereof. Furthermore, the present invention is concerned with a method of preventing or treating angiogenesis-associated pathologies which comprises administering to a subject in need of such treatment for therapy or

prophylaxis an effective amount of lycopene. The present invention is also concerned with certain novel solid galenical formulations comprising lycopene.

In a further and preferred embodiment of the invention, lycopene is used together with vitamin E and/or vitamin C. Most preferred is a combination of lycopene, vitamin E and vitamin C. The term vitamin E as used herein includes racemic vitamin E (D,L-α-tocopherol) or natural vitamin E, as well as derivatives thereof which have biological vitamin E activity, e.g. carboxylic acid esters, such as vitamin E acetate, propionate, butyrate or succinate. The term vitamin C as used herein includes derivatives thereof which have biological vitamin C activity, e.g. esters and salts, such as sodium ascorbate, sodium ascorbyl phosphate, and ascorbyl palmitate. In a further embodiment of the invention, one or more of the following components can be used together with these active ingredients:

(a) Astaxanthin ((3S, 3'S)-3, 3'-dihydroxy-β, β-carotene-4, 4'-dione) and/or one or more isomers and/or monoesters and/or diesters, preferably esters of saturated alkanoic acids, such as acetic, propionic, palmitic, stearic, and succinic acid, mono-unsaturated fatty acids, such as oleic acid, and poly-unsaturated fatty acids, such as linolic, linoleic, docosahexaenoic, and arachidonic acid;

(b) β-Carotene and/or one or more isomers thereof;

(c) β-Cryptoxanthin ((3R)-β, β-carotene-3-ol) and/or one or more isomers or esters thereof, preferably esters of saturated alkanoic acids, such as acetic, propionic, palmitic, stearic, and succinic acid, mono-unsaturated fatty acids, such as oleic acid, and poly-unsaturated fatty acids, such as linolic, linoleic, docosahexaenoic, and arachidonic acid;

(d) (-)-Epigallocatechin gallate (EGCG) and/or (-)-epicatechin gallate (ECG) and/or one or more derivatives thereof;

(e) Genistein aglycone (4', 5, 7-trihydroxyisoflavone) and/or one or more derivatives thereof (genistein glucosides, genistein sulfates, genistein glucuronides);

(f) Lutein ((3R, 3'R, 6'R)-β, ε, carotene-3, 3'-diol) and/or one or more isomers and/or monoesters and/or diesters, preferably esters of saturated alkanoic acids, such as acetic, propionic, palmitic, stearic, and succinic acid, mono-unsaturated fatty acids, such as

oleic acid, and poly-unsaturated fatty acids, such as linolic, linoleic, docosahexaenoic, and arachidonic acid, thereof;

(g) Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyrano-4-one) and/or dihydroquercetin and/or one or more derivatives thereof (quercetine glucosides, quercetin glucuronides, quercetine sulphates, methylquercetins (isohamnetin (3'-O-methylquercetin), tamarixetin(4'-O-methylquercetin));

(h) Myricetin and/or one or more derivatives thereof;

(i) Resveratrol (*cis*-3, 4', 5-trihydroxystilbene and/or *trans*-3, 4', 5-trihydroxystilbene) and/or one or more derivatives thereof (resveratrol glucosides, resveratrol sulfates, resveratrol glucuronides);

(j) Rhizoxin and/or one or more derivatives thereof (palmitoyl rhizoxin);

(k) Silymarin (extract from *Silybum marianum*) and/or one or more derivatives thereof (silymarin dihemisuccinate sodium salt) and/or one or more of its four main components (silybin [synonymous with silibinin, and sometimes incorrectly called silybinin] and/or isosilybin and/or silydianin and/or silychristin) and/or one or more derivatives thereof (silybin-dihemisuccinate, disilybin, silybin-phosphatidylcholine complex, silybin-phosphate);

(l) Vitamin A and/or one or more derivatives thereof (all-*trans* retinol or all-*trans* retinyl acetate or all-*trans* retinyl palmitate);

(m) Vitamin D2 or vitamin D3 or 1α, 25-dihydroxyvitamin D3 or 25-hydroxyvitamin D3 or 1α, 24R, 25-trihydroxyvitamin D3;

(n) Zeaxanthin ((3R, 3'R)-β, β-carotene-3, 3'-diol) and/or one or more isomers and stereo-isomers (preferably mesozeaxanthin, 3R,3'S-zeaxanthin) and/or monoesters and/or diesters, preferably esters of saturated alkanoic acids, such as acetic, propionic, palmitic, stearic, and succinic acid, mono-unsaturated fatty acids, such as oleic acid, and poly-unsaturated fatty acids, such as linolic, linoleic, docosahexaenoic, and arachidonic acid, thereof;

(o) Apigenin and/or one or more derivatives thereof;

(p) Carnosic acid and/or one or more derivatives thereof;

(q) Carnosol and/or one or more derivatives thereof;

(r) Depudecin and/or one or more derivatives thereof;

(s) Eponemycin and/or one or more derivatives thereof;

(t) Dihydroeponemycin and/or one or more derivatives thereof;

(u) Epoxomicin and/or one or more derivatives thereof;

(v) Ergosterol and/or one or more derivatives thereof;

(w) Fisetin and/or one or more derivatives thereof;

(x) Fumagillin and/or one or more derivatives thereof;

(y) Lactacystin and/or one or more derivatives thereof;

(z) Luteolin and/or one or more derivatives thereof;

(aa) Motuporamine C and/or one or more derivatives thereof;

(bb) Ovalicin and/or one or more derivatives thereof;

(cc) Radicicol and/or one or more derivatives thereof;

(dd) Curcumin and/or one or more derivatives (demethoxy-curcumin, bis-demethoxycurcumin, sodium curcumionate, bis-demethylcurcumin, tetrahydrocurcumin, diacteylcurcumin, triethylcurcumin) thereof;

(ee) Squalamine and/or one or more derivatives thereof;

(ff) Isoliquiritin, isoliquiritigenin, liquiritigenin and/or one or more derivatives thereof;

(gg) Very-long-chain omega-3 fatty acides (eicosapentaenoic acid [C20: 5, omega-3], decosahexaenoic acid [C22: 6, omega-3], polyunsaturated ω-3 fatty acids);

(hh) Shark cartilage extract.

(ii) Glucosinolate derivatives (Methylsulfinylalkyl glucosinolates [1-methylsulfinylmethyl glucosinolate, 2-methylsulfinylethyl glucosinolate, 3-methylsulfinylpropyl glucosinolate (glucoiberin), 4-methylsulfinylbutyl glucosinolate (glucoraphanin), 5-methylsulfinylpentyl glucosinolate (glucoalysin), 6-methylsulfinylhexyl glucosinolate, 7-methylsulfinylheptyl glucosinolate, 8-methylsulfinyloctyl glucosinolate, 9-methylsulfinylnonyl glucosinolate, 10-methylsulfinyldodecyl glucosinolate] or allyl glucosinolate (sinigrin) or phenylethyl glucosinolate (gluconasturtiin) or 3-butenyl glucosinolate (gluconapin) or indol-3-ylmethyl glucosinolate (glucobrassicin) or derivatives thereof [N-methoxyindol-3-ylmethyl glucosinolate (neoglucobrassicin), 4-hydroxyindol-3-ylmethyl glucosinolate (4-OH glucobrassicin), 4-methoxyindol-3-ylmethyl glucosinolate (4-CH_3O glucobrassicin)]).

(jj) Isothiocyanate derivatives (Methylsulfinylalkyl isothiocyanate [1-methylsulfinylmethyl isothiocyanate, 2-methylsulfinylethyl isothiocyanate, 3-methylsulfinylpropyl isothiocyanate, 4-methylsulfinylbutyl isothiocyanate (sulforaphane), 5-methylsulfinylpentyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate (6-HITC), 7-methylsulfinylheptyl isothiocyanate, 8-methylsulfinyloctyl isothiocyanate, 9-methylsulfinylnonyl isothiocyanate, 10-methylsulfinyldodecyl isothiocyanate] or allyl isothiocyanate or phenylethyl isothiocyanate (PEITC) or 3-butenyl isothiocyanate or indol-3-ylmethylisothiocyanate or derivatives thereof (N-methoxy indol-3-ylmethylisothiocyanate, 4-hydroxy indol-3-ylmethylisothiocyanate, 4-methoxy indol-3-ylmethylisothiocyanate) or 3-indolmethanol (indol-3-carbinol, I3C).

Examples of angiogenesis associated pathologies comprise Hodgkin lymphoma, non-Hodgkin lymphoma, lymphosarcoma, lymphoblastoid leukemia, acute lymphatic leukemia, acute myeloic leukemia, chronic myeloic leukemia, chronic lymphatic leukemia, hemangioma, hemangioendothelioma, hemangiopericytoma, hemangiosarcoma, Kaposi sarcoma, osteosarcoma, fibrosarcoma, oesophageal squamous cell carcinoma, pancreatic carcinoma, gastrointestinal tumors, colon carcinoma, rectum carcinoma, stomach carcinoma, lymphangiosarcoma, brain tumors, neuroblastoma, schwannoma, pheochromocytoma, lung carcinoma, head and neck squamous cell carcinoma, melanoma, non-melanoma skin carcinoma, leiomyomas, leiomyosarcomas, mammary carcinoma, ovarian cancer, endometrial carcinoma, bladder carcinoma, cervix carcinoma, renal carcinoma, prostate carcinoma, metastasis formation, asthma, rheumatoid arthritis,

synovitis, degenerative or inflammatory bone and cartilage destruction, non-rheumatoid arthritis, tendosynovitis, inflammatory pseudotumor, diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, retinopathy of prematurity, choroidal and other intraocular diseases, keratoconjunctivitis, gingivitis, periodontal disease, epulis, gastritis, hepatitis, liver regeneration, chronic pancreatitis, tonsillitis, obesity, leukomalacia, rhinitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, interstitial pulmonary fibrosis, neurodermitis, psoriasis, thyroiditis, thyroid enlargement, endometriosis, and glomerulonephritis. Of primary interest for treatment in accordance with the present invention are prostate carcinoma, mammary carcinoma, bladder carcinoma, lung carcinoma, pancreatic carcinoma, melanoma, non-Hodgkin lymphoma, colon/rectum carcinomas, endometrial carcinoma, age-related macular degeneration, prostatitis, diabetic retinopathy, psoriasis, rheumatoid arthritis, non-rheumatoid arthritis and gastritis.

For the primary and secondary prevention and coadjuvant treatment of angiogenesis-associated pathologies in accordance with the present invention lycopene is administered to the subject in need of such treatment, i.e. humans, pets or farm animals in an amount of from about 0.0005 mg/kg body weight to about 5 mg/kg body weight per day. When vitamin E or derivatives thereof is co-administered the daily dosage is from about 0.1 mg/kg body weight to about 15 mg/kg body weight, based on tocopherol. When vitamin C or derivative thereof is co-administered the daily dosage is from about 0.2 mg/kg body weight to about 30 mg/kg body weight, based on ascorbic acid. Other components may be co-administered within dosage ranges set forth below:

Astaxanthin	0.001mg/kg	to	5mg/kg
β-Carotene	0.001mg/kg	to	5mg/kg
β-Cryptoxanthin	0.001mg/kg	to	5mg/kg
(-)-epigallocatechin gallate (EGCG) or (-)-epicatechin gallate (ECG) or equimolar amounts of derivatives	0.5mg/kg	to	15mg/kg

Genistein aglycone	0.015mg/kg	to	6mg/kg
Lutein	0.001mg/kg	to	5mg/kg
Quercetin	0.001mg/kg	to	300mg/kg
Myricetin	0.001mg/kg	to	300mg/kg
Resveratrol	0.01mg/kg	to	1.5mg/kg
or equimolar amounts of derivatives			
Rhizoxin	0.001mg/kg	to	20mg/kg
Palmitoyl Rhizoxin	0.001mg/kg	to	20mg/kg
Silymarin	0.01mg/kg	to	100mg/kg
Silybin	0.01mg/kg	to	100mg/kg
or equimolar amounts of derivatives			
Isosilybin	0.01mg/kg	to	100mg/kg
or equimolar amounts of derivatives			
Silydianin	0.01mg/kg	to	100mg/kg
or equimolar amounts of derivatives			
Silychristin	0.01mg/kg	to	100mg/kg
or equimolar amounts of derivatives			
All-*trans* Retinol	3µg/kg	to	100µg/kg
All-*trans* Retinyl acetate	3.5µg/kg	to	115µg/kg
All-*trans* Retinol palmitate	5.5µg/kg	to	180µg/kg
Vitamin D2 (Ergocalciferol)	0.1ng/kg	to	10µg/kg
Vitamin D3 (Cholecalciferol)	0.1ng/kg	to	10µg/kg
1α, 25-Dihydroxyvitamin D3	0.1ng/kg	to	0.5µg/kg

25-Hydroxyvitamin D3	0.1ng/kg	to	10μg/kg
1α, 24R, 25-Trihydroxyvitamin D3	0.1ng/kg	to	0.5μg/kg
Zeaxanthin	0.001mg/kg	to	5mg/kg
Apigenin	0.01mg/kg	to	500mg/kg
Carnosic acid	0.01mg/kg	to	250mg/kg
Carnosol	0.01mg/kg	to	250mg/kg
Depudecin	0.01mg/kg	to	500mg/kg
Eponemycin	0.01mg/kg	to	500mg/kg
Dihydroeponemycin	0.01mg/kg	to	500mg/kg
Epoxomicin	0.01mg/kg	to	500mg/kg
Ergosterol	0.1mg/kg	to	2000mg/kg
Fisetin	0.01mg/kg	to	500mg/kg
Fumagillin	0.1mg/kg	to	300mg/kg
Lactacystin	0.01mg/kg	to	250mg/kg
Luteolin	0.01mg/kg	to	100mg/kg
Motuporamine C	0.1mg/kg	to	500mg/kg
Ovalicin	0.1mg/kg	to	250mg/kg
Radicicol	0.1mg/kg	to	1000mg/kg
Curcumin or equimolar amounts of derivatives	0.1mg/kg	to	200mg/kg
Squalamine	0.001	to	200mg/kg

Isoliquiritin	1ng/kg	to	1mg/kg
Isoliquiritigenin	1ng/kg	to	1mg/kg
Very-long-chain omega-3 fatty acides	0.001g/kg	to	0.05g/kg
Shark cartilage extract	0.001g/kg	to	0.1g/kg
Glucosinolate derivatives e.g. 4-methylsulfinylbutyl glucosinolate (glucoraphanin)	0.01mg/kg	to	200mg/kg
Isothiocyanate derivatives or I3C e.g. 4-methylsulfinylbutyl isothiocyanate (sulforaphane)	0.001mg/kg	to	200mg/kg

Lycopene, optionally together with the vitamins E and C as well as compounds (a) to (jj) can find use in accordance with the present invention for the completion of human nutrition, nutrition of pets and farm animals.

Said compounds may be provided as the active ingredient in compositions, preferably for enteral application, which may be solid or liquid galenical formulations, dietary compositions or animal feed compositions. Examples of solid galenical formulations are tablets, capsules (e.g. hard or soft shell gelatin capsules), pills, sachets, powders, granules and the like which contain the active ingredient together with conventional galenical carriers. Any conventional carrier material can be utilized. The carrier material can be organic or inorganic inert carrier material suitable for oral administration. Suitable carriers include water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, and the like. Additionally, additives such as flavouring agents, preservatives, stabilizers, emulsifying agents, buffers and the like may be added in accordance with accepted practices of pharmaceutical compounding. They may also be used in dietary compositions which may be a food, a food premix or a fortified food or a beverage. While the individual active ingredients are suitably administered in a single composition they may also be administered in individual dosage units.

Preferably lycopene is used in accordance with the present invention together with vitamin E or vitamin E and vitamin C. Preferred additional components are the active ingredients

(a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), and/or (n); more preferably the active ingredients (b), (d), (e), (f), (g), (h), (i), (j), (k), and/or (n).

Particularly preferred is the administration of the following active ingredients :

Lycopene, in a concentration so that the daily consumption by a human adult is in the range of from 0.25mg/day to 50mg/day, preferably from 1mg/day to 30mg/day; and/or

Vitamin E or its derivative, in a concentration so that the daily consumption by a human adult is in the range of from 15mg/day to 600mg/day; and/or

Vitamin C or its derivative, in a concentration so that the daily consumption by a human adult is in the range of from 50mg/day to 1000mg/day; and/or

β-Carotene, in a concentration so that the daily consumption by a human adult is in the range of from 0.1 mg/day to 20mg/day, preferably from 2mg/day to 10 mg/day; and/or

(-)-Epigallocatechin gallate (EGCG), in a concentration so that the daily consumption by a human adult is in the range of from 50mg/day to 500mg/day; and/or

Genistein, in a concentration so that the daily consumption by a human adult is in the range of from 20mg/day to 200mg/day; and/or

Lutein, in a concentration so that the daily consumption by a human adult is in the range of from 0.1mg/day to 50mg/day, preferably from 0.25mg/day to 30mg/day; and/or

Quercetin, in a concentration so that the daily consumption by a human adult is in the range of from 1mg/day to 500mg/day; and/or

Myricetin, in a concentration so that the daily consumption by a human adult is in the range of from 1mg/day to 500mg/day; and/or

Resveratrol, in a concentration so that the daily consumption by a human adult is in the range of from 5 mg/day to 50 mg/day; and/or

Silymarin (extract from *Silybum marianum*) or its four main components (silybin and/or isosilybin and/or silydianin and/or silychristin), in a concentration so that the daily consumption by a human adult of Silymarin or its four main components (silybin,

isosilybin, silydianin, silychristin), respectively, is in the range of from 1mg/day to 1000mg/day, preferably from 50mg/day to 800mg/day; and/or

Zeaxanthin, in a concentration so that the daily consumption by a human adult is in the range of from 0.1mg/day to 50mg/day, preferably from 0.25mg/day to 30mg/day.

Typical examples of galenical formulations for use in accordance with the present invention are given below. The Examples are for the purpose of illustrating the invention and are not intended to limit the scope of the invention in any way.

Example 1

A tablet for the coadjuvant treatment of prostate carcinoma is formulated to contain 5 mg of lycopene, 200 mg of vitamin E, 250 mg of vitamin C, 37.5 mg of resveratrol, and 50 mg of quercetin. The daily dose corresponds to two such tablets.

Example 2

A tablet for the primary prevention of gastritis is formulated to contain 3.5 mg of lycopene, 150 mg of vitamin E, 100 mg of vitamin C, 25 mg of resveratrol, 2.5 mg of lutein and 3.5 mg of β-carotene. The daily dose corresponds to two such tablets.

Example 3

A tablet for the primary prevention of age-related macular degeneration is formulated to contain 3.5 mg of lycopene, 50 mg of vitamin E, 50 mg of vitamin C, 5 mg of lutein, 5 mg of zeaxanthin and 5 mg of β-carotene. The daily dose corresponds to two such tablets.

Example 4

A patient weighing 70 kg and receiving conventional prostate carcinoma therapy is administered, for the duration of carcinoma therapy, 10 mg of lycopene, 200 mg of vitamin E, 250 mg of vitamin C, 37.5 mg of resveratrol, and 50 mg of quercetin per day in a single dosage unit, e.g. by administration of 2 tablets of Example 1, or in individual dosage units of the components.

Example 5

A patient weighing 70 kg with a history of episodes of gastritis is administered, prophylactically, 7 mg of lycopene, 300 mg of vitamin E, 200 mg of vitamin C, 50 mg of resveratrol, 5 mg of lutein and 7 mg of β-carotene per day in a single dosage unit, e.g. by administration of 1 tablet of Example 1, or in individual dosage units of the components.

Example 6

A patient weighing 70 kg who is prone to age-related macular degeneration is administered 7 mg of lycopene, 100 mg of vitamin E, 100 mg of vitamin C, 10 mg of lutein, 10 mg of zeaxanthin and 10 mg of β-carotene per day in a single dosage unit, e.g. by administration of 1 tablet of Example 1, or in individual dosage units of the components.

What is claimed is:

1. The use of lycopene in the manufacture of a composition for the primary and secondary prevention of angiogenesis-associated pathologies and coadjuvant treatment thereof.

2. The use as in claim 1 of lycopene in combination with vitamin E.

3. The use as in claim 1 of lycopene in combination with vitamin E and vitamin C.

4. The use as in any one of claims 1 to 3 of lycopene in combination with one or more compounds selected from β-carotene, (-)-epigallocatechin gallate, genistein, lutein, quercetin, myricetin, resveratrol, silymarin or its four main components (silybin and/or isosilybin and/or silydianin and/or silychristin), and zeaxanthin.

5. The use as in any one of claims 1 to 3 of lycopene in combination with one or more compounds selected from

astaxanthin, β-carotene, β-cryptoxanthin, (-)-epigallocatechin gallate (EGCG) or (-)-epicatechin gallate (ECG) or equimolar amounts of derivatives, genistein aglycone, lutein, quercetin, myricetin, resveratrol or equimolar amounts of derivatives, rhizoxin, palmitoyl rhizoxin, silymarin, silybin or equimolar amounts of derivatives, isosilybin or equimolar amounts of derivatives, silydianin or equimolar amounts of derivatives, silychristin or equimolar amounts of derivatives, all-*trans* retinol, all-*trans* retinyl acetate, all-*trans* retinol palmitate, vitamin D2 (ergocalciferol), vitamin D3, (cholecalciferol), 1α, 25-dihydroxy-vitamin D3, 25-hydroxyvitamin D3, 1α, 24R, 25-trihydroxyvitamin D3, zeaxanthin, apigenin, carnosic acid, carnosol, depudecin, eponemycin, dihydroeponemycin, epoxomicin, ergosterol, fisetin, fumagillin, lactacystin, luteolin, motuporamine C, ovalicin, radicicol, curcumin or equimolar amounts of derivatives, squalamine, isoliquiritin, isoliquiritigenin, very-long-chain omega-3 fatty acides, shark cartilage extract, glucosinolate derivatives: methylsulfinylalkyl glucosinolates (1-methylsulfinylmethyl glucosinolate, 2-methylsulfinylethyl glucosinolate, 3-methylsulfinylpropyl glucosinolate (glucoiberin), 4-methylsulfinylbutyl glucosinolate (glucoraphanin), 5-methylsulfinylpentyl glucosinolate (glucoalysin), 6-methylsulfinylhexyl glucosinolate, 7-methylsulfinylheptyl glucosinolate, 8-methylsulfinyloctyl glucosinolate, 9-methylsulfinylnonyl glucosinolate, 10-methylsulfinyldodecyl glucosinolate) or allyl glucosinolate (sinigrin) or indol-3-ylmethyl glucosinolate (glucobrassicin) or derivatives thereof, (N-methoxyindol-3-ylmethyl glucosinolate (neoglucobrassicin), 4-hydroxyindol-3-ylmethyl glucosinolate (4-OH glucobrassicin), 4-methoxyindol-3-ylmethyl glucosinolate (4-CH_3O glucobrassicin)) or phenylethyl glucosinolate (gluconasturtiin) or 3-butenyl glucosinolate (gluconapin)), isothiocyanate derivatives: methylsulfinylalkyl isothiocyanates (1-methylsulfinylmethyl isothiocyanate, 2-methylsulfinylethyl isothiocyanate, 3-methylsulfinylpropyl isothiocyanate, 4-methylsulfinylbutyl isothiocyanate (sulforaphane), 5-methylsulfinyl-pentyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate (6-HITC), 7-methylsulfinyl-heptyl isothiocyanate, 8-methylsulfinyloctyl isothiocyanate, 9-methylsulfinylnonyl-isothiocyanate, 10-methylsulfinyldodecyl isothiocyanate) or allyl isothiocyanate, indol-3-ylmethylisothiocyanate, N-methoxy indol-3-ylmethylisothiocyanate, 4-hydroxy indol-3-ylmethylisothiocyanate, 4-methoxy indol-3-ylmethylisothiocyanate, 3-indolmethanol, phenylethyl isothiocyanate (PEITC), and 3-butenyl isothiocyanate.

6. The use as in any one of claims 1 to 5 wherein the angiogenesis-associated pathologies are Hodgkin lymphoma, non-Hodgkin lymphoma, lymphosarcoma, lymphoblastoid leukemia, acute lymphatic leukemia, acute myeloic leukemia, chronic myeloic leukemia, chronic lymphatic leukemia, hemangioma, hemangioendothelioma, hemangiopericytoma, hemangiosarcoma, Kaposi sarcoma, osteosarcoma, fibrosarcoma, oesophageal squamous

cell carcinoma, pancreatic carcinoma, gastrointestinal tumors, colon carcinoma, rectum carcinoma, stomach carcinoma, lymphangiosarcoma, brain tumors, neuroblastoma, schwannoma, pheochromocytoma, lung carcinoma, head and neck squamous cell carcinoma, melanoma, non-melanoma skin carcinoma, leiomyomas, leiomyosarcomas, mammary carcinoma, ovarian cancer, endometrial carcinoma, bladder carcinoma, cervix carcinoma, renal carcinoma, prostate carcinoma, metastasis formation, asthma, rheumatoid arthritis, synovitis, degenerative or inflammatory bone and cartilage destruction, non-rheumatoid arthritis, tendosynovitis, inflammatory pseudotumor, diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, retinopathy of prematurity, choroidal and other intraocular diseases, keratoconjunctivitis, gingivitis, periodontal disease, epulis, gastritis, hepatitis, liver regeneration, chronic pancreatitis, tonsillitis, obesity, leukomalacia, rhinitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, interstitial pulmonary fibrosis, neurodermitis, psoriasis, thyroiditis, thyroid enlargement, endometriosis, and glomerulonephritis.

7. The use as in any one of claims 1 to 5 wherein the angiogenesis-associated pathologies are prostate carcinoma, mammary carcinoma, bladder carcinoma, lung carcinoma, pancreatic carcinoma, melanoma, non-Hodgkin lymphoma, colon/rectum carcinomas, endometrial carcinoma, age-related macular degeneration, prostatitis, diabetic retinopathy, psoriasis, rheumatoid arthritis, non-rheumatoid arthritis and gastritis.

8. The use as in any one of claims 1 to 5 wherein the angiogenesis-associated pathology is prostate carcinoma.

9. The use as in any one of claims 1 to 5 wherein the angiogenesis-associated pathology is mammary carcinoma.

10. The use as in any one of claims 1 to 5 wherein the angiogenesis-associated pathology is gastritis.

11. The use as in any one of claims 1 to 5 wherein the angiogenesis-associated pathology is age-related macular degeneration.

12. The use as in any one of claims 1 to 11 wherein the composition is a solid or liquid galenical formulation, a dietary composition or an animal feed composition.

13. The use as in claim 12 wherein a dosage unit of said solid galenical formulation contains from about 0.25 mg to about 50 mg of lycopene.

14. The use as in claim 12 wherein said liquid galenical formulation contains from about 0.1 mg to about 100 mg of lycopene per ml.

15. The use as in claim 12 wherein said dietary composition or animal feed composition contains from about 0.025 mg to about 5 mg of lycopene per g.

16. The use as in claim 13 wherein a dosage unit of said solid galenical formulation further contains from about 15 mg to about 500 mg of vitamin E.

17. The use as in claim 14 wherein said liquid galenical formulation further contains from about 10 mg to about 300 mg of vitamin E per ml.

18. The use as in claim 15 wherein said dietary composition or animal feed composition further contains from about 1.5 mg to about 30 mg of vitamin E per g.

19. The use as in claim 13 or 16 wherein a dosage unit of said solid galenical formulation further contains from about 50 mg to about 500 mg of vitamin C.

20. The use as in claim 14 or 17 wherein said liquid galenical formulation further contains from about 50 mg to about 100 mg of vitamin C per ml.

21. The use as in claim 15 or 18 wherein said dietary composition or animal feed composition further contains from about 5 mg to about 50 mg of vitamin C per g.

22. The use as in any one of claims 1 to 21 wherein the composition further contains one or more active ingredients selected from the group of β-carotene, (-)-epigallocatechin gallate, genistein, lutein, quercetin, resveratrol, silymarin or one or more of its four main components (silybin and/or isosilybin and/or silydianin and/or silychristin), and zeaxanthin.

23. The use as in any one of claims 1 to 21 wherein the composition further contains one or more active ingredients selected from

astaxanthin, β-carotene, β-cryptoxanthin, (-)-epigallocatechin gallate (EGCG) or (-)-epicatechin gallate (ECG) or equimolar amounts of derivatives, genistein aglycone, lutein, quercetin, myricetin, resveratrol or equimolar amounts of derivatives, rhizoxin, palmitoyl rhizoxin, silymarin, silybin or equimolar amounts of derivatives, isosilybin or equimolar amounts of derivatives, silydianin or equimolar amounts of derivatives, silychristin or

equimolar amounts of derivatives, all-*trans* retinol, all-*trans* retinyl acetate, all-*trans* retinol palmitate, vitamin D2 (ergocalciferol), vitamin D3, (cholecalciferol), 1α, 25-dihydroxy-vitamin D3, 25-hydroxyvitamin D3, 1α, 24R, 25-trihydroxyvitamin D3, zeaxanthin, apigenin, carnosic acid, carnosol, depudecin, eponemycin, dihydroeponemycin, epoxomicin, ergosterol, fisetin, fumagillin, lactacystin, luteolin, motuporamine C, ovalicin, radicicol, curcumin or equimolar amounts of derivatives, squalamine, isoliquiritin, isoliquiritigenin, very-long-chain omega-3 fatty acides, shark cartilage extract, glucosinolate derivatives: methylsulfinylalkyl glucosinolates (1-methylsulfinylmethyl glucosinolate, 2-methylsulfinylethyl glucosinolate, 3-methylsulfinylpropyl glucosinolate (glucoiberin), 4-methylsulfinylbutyl glucosinolate (glucoraphanin), 5-methylsulfinylpentyl glucosinolate (glucoalysin), 6-methylsulfinylhexyl glucosinolate, 7-methylsulfinylheptyl glucosinolate, 8-methylsulfinyloctyl glucosinolate, 9-methylsulfinylnonyl glucosinolate, 10-methylsulfinyldodecyl glucosinolate) or allyl glucosinolate (sinigrin) or indol-3-ylmethyl glucosinolate (glucobrassicin) or derivatives thereof, (N-methoxyindol-3-ylmethyl glucosinolate (neoglucobrassicin), 4-hydroxyindol-3-ylmethyl glucosinolate (4-OH glucobrassicin), 4-methoxyindol-3-ylmethyl glucosinolate (4-CH_3O glucobrassicin)) or phenylethyl glucosinolate (gluconasturtiin) or 3-butenyl glucosinolate (gluconapin)), isothiocyanate derivatives: methylsulfinylalkyl isothiocyanates (1-methylsulfinylmethyl isothiocyanate, 2-methylsulfinylethyl isothiocyanate, 3-methylsulfinylpropyl isothiocyanate, 4-methylsulfinylbutyl isothiocyanate (sulforaphane), 5-methylsulfinyl-pentyl isothiocyanate, 6-methylsulfinylhexyl isothiocyanate (6-HITC), 7-methylsulfinyl-heptyl isothiocyanate, 8-methylsulfinyloctyl isothiocyanate, 9-methylsulfinylnonyl-isothiocyanate, 10-methylsulfinyldodecyl isothiocyanate) or allyl isothiocyanate, indol-3-ylmethylisothiocyanate, N-methoxy indol-3-ylmethylisothiocyanate, 4-hydroxy indol-3-ylmethylisothiocyanate, 4-methoxy indol-3-ylmethylisothiocyanate, 3-indolmethanol, phenylethyl isothiocyanate (PEITC), and 3-butenyl isothiocyanate.

24. The use as in any one of claims 1 to 23 in the manufacture of a solid galenical formulation for the coadjuvant treatment of prostate carcinoma containing lycopene in combination with vitamin E, vitamin C, resveratrol, and quercetin in one dosage unit.

25. The use as in any one of claims 1 to 23 in the manufacture of a solid galenical formulation for the primary prevention of gastritis containing lycopene in combination with vitamin E, vitamin C, resveratrol, and β-carotene in one dosage unit.

26. The use as in any one of claims 1 to 23 in the manufacture of a solid galenical formulation for the primary prevention of age-related macular degeneration containing lycopene in combination with vitamin E, vitamin C, lutein, zeaxanthin, and β-carotene in one dosage unit.

27. A solid galenical formulation containing per dosage unit (with 2 dosage units per day) 5 mg of lycopene, 200 mg of vitamin E, 250 mg of vitamin C, 37.5 mg of resveratrol, and 50 mg of quercetin.

28. A solid galenical formulation containing per dosage unit (with 2 dosage units per day). 3.5 mg of lycopene, 150 mg of vitamin E, 100 mg of vitamin C, 25 mg of resveratrol, 2.5 mg of lutein and 3.5 mg of β-carotene.

29. A solid galenical formulation containing per dosage unit (with 2 dosage units per day) 3.5 mg of lycopene, 50 mg of vitamin E, 50 mg of vitamin C, 5 mg of lutein, 5 mg of zeaxanthin and 5 mg of β-carotene.

30. A method of preventing or treating angiogenesis-associated pathologies which comprises administering to a subject in need of such treatment for therapy or prophylaxis an effective amount of lycopene.

31. A method as in claim 30 wherein the angiogenesis-associated pathologies are Hodgkin lymphoma, non-Hodgkin lymphoma, lymphosarcoma, lymphoblastoid leukemia, acute lymphatic leukemia, acute myeloic leukemia, chronic myeloic leukemia, chronic lymphatic leukemia, hemangioma, hemangioendothelioma, hemangiopericytoma, hemangiosarcoma, Kaposi sarcoma, osteosarcoma, fibrosarcoma, oesophageal squamous cell carcinoma, pancreatic carcinoma, gastrointestinal tumors, colon carcinoma, rectum carcinoma, stomach carcinoma, lymphangiosarcoma, brain tumors, neuroblastoma, schwannoma, pheochromocytoma, lung carcinoma, head and neck squamous cell carcinoma, melanoma, non-melanoma skin carcinoma, leiomyomas, leiomyosarcomas, mammary carcinoma, ovarian carcinoma, endometrial carcinoma, bladder carcinoma, cervix carcinoma, renal carcinoma, prostate carcinoma, metastasis formation, asthma, rheumatoid arthritis, synovitis, degenerative or inflammatory bone and cartilage destruction, non-rheumatoid arthritis, tendosynovitis, inflammatory pseudotumor, diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, retinopathy of prematurity, choroidal and other intraocular diseases, keratoconjunctivitis, gingivitis,

periodontal disease, epulis, gastritis, hepatitis, liver regeneration, chronic pancreatitis, tonsillitis, obesity, leukomalacia, rhinitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, interstitial pulmonary fibrosis, neurodermitis, psoriasis, thyroiditis, thyroid enlargement, endometriosis, or glomerulonephritis.

32. A method as in claim 30 wherein the angiogenesis-associated pathologies are prostate carcinoma, mammary carcinoma, bladder carcinoma, lung carcinoma, pancreatic carcinoma, melanoma, non-Hodgkin lymphoma, colon/rectum carcinomas, endometrial carcinoma, age-related macular degeneration, prostatitis, diabetic retinopathy, psoriasis, rheumatoid arthritis, non-rheumatoid arthritis, or gastritis.

33. A method as in claim 30 wherein the angiogenesis-associated pathology is prostate carcinoma.

34. A method as in claim 30 wherein the angiogenesis-associated pathology is mammary carcinoma.

35. A method as in claim 30 wherein the angiogenesis-associated pathology is gastritis.

36. A method as in claim 30 wherein the angiogenesis-associated pathology is age-related macular degeneration.

37. A method as in any one of claims 30 to 36 wherein about 0.25 mg to about 50 mg of lycopene are administered per day to a human adult.

38. A method as in any one of claims 30 to 37 wherein about 1 mg to about 30 mg of lycopene are administered per day to a human adult.

39. A method as in any one of claims 30 to 38 wherein, additionally, about 15 mg to about 600 mg of vitamin E are administered per day to a human adult.

40. A method as in claim 28 to 37 wherein, additionally, about 50 to about 1000 mg of vitamin C are administered per day to a human adult.

41. A method for the coadjuvant treatment of prostate carcinoma which comprises administering to a human adult lycopene in combination with vitamin E, vitamin C, resveratrol, and quercetin.

42. A method for the primary prevention of gastritis which comprises administering to a human adult lycopene, vitamin E, vitamin C, resveratrol, lutein, and β-carotene.

43. A method for the primary prevention of age-related macular degeneration which comprises administering to a human adult lycopene, vitamin E, vitamin C, lutein, of zeaxanthin, and β-carotene.

44. A method as in claim 39, wherein 10 mg of lycopene, 400 mg of vitamin E, 500 mg of vitamin C, 75 mg of resveratrol, and 100 mg of quercetin are administered to a human adult per day.

45. A method as in claim 40, wherein 7 mg of lycopene, 300 mg of vitamin E, 200 mg of vitamin C, 50 mg of resveratrol, 5 mg of lutein, and 7 mg of β-carotene are administered to a human adult per day.

46. A method as in claim 41, wherein 7 mg of lycopene, 100 mg of vitamin E, 100 mg of vitamin C, 10 mg of lutein, 10 mg of zeaxanthin, and 10 mg of β-carotene are administered to a human adult per day.

47. The invention substantially as described hereinbefore, especially with reference to the Examples.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01149

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/015 A61K31/355 A61K31/375 A23L1/302 A61K31/05
A61P35/00 A61P27/00 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 26668 A (UNILEVER PLC ;LEVER HINDUSTAN LTD (IN); SCHROEDER FRITZ H (NL); TI) 19 April 2001 (2001-04-19) page 8, line 20-31; claims 1,2,10,12,17	1,2,4-8, 12,13, 22,23, 30-33, 37,38
X	WO 02 05827 A (CLAYTON PAUL RODNEY ;DEXTER DAVID (GB); FORUM BIOSCIENCE (GB); ROO) 24 January 2002 (2002-01-24) page 1, line 11-14 page 2, line 30 page 8, line 7-14 claims 12,13	1-7,12, 13,22, 23, 30-33, 37,38

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2003	19/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01149

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 89542 A (SOLDATI FABIO ;PHARMATON SA (CH)) 29 November 2001 (2001-11-29) page 3, line 15-17 page 6, line 15,16,24-30; claims 1-6,12; examples	1-8,12, 13, 22-25, 30-34,37
X	US 6 103 756 A (GORSEK WAYNE F) 15 August 2000 (2000-08-15) column 1, line 15-19,56-62; claims 1-3; table 1	1-7, 11-13, 22,23, 26, 30-33,36
X	WO 96 40092 A (HOWARD FOUNDATION ;HOWARD ALAN NORMAN (GB); BONE RICHARD ANDREW (U) 19 December 1996 (1996-12-19) page 5, line 28 -page 6, line 12 claims 15,24	1-7, 11-13, 22,23, 26, 30-33,36
X	GERSTER H: "THE POTENTIAL ROLE OF LYCOPENE FOR HUMAN HEALTH" JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, AMERICAN COLLEGE OF NUTRION, WILMINGTON, NC, US, vol. 16, no. 2, April 1997 (1997-04), pages 109-126, XP008005033 ISSN: 0731-5724 page 117, column 1-2	1,6-8, 30-34
X	MCCARTY M F: "Suppression of dolichol synthesis with isoprenoids and statins may potentiate the cancer-retardant efficacy of IGF-I down-regulation." MEDICAL HYPOTHESES. SCOTLAND JAN 2001, vol. 56, no. 1, January 2001 (2001-01), pages 12-16, XP009010097 ISSN: 0306-9877 page 137, column 2 page 14, column 1-2	1,6-8, 30-34
P,X	US 6 350 776 B1 (AZZI ANGELO MANFREDO) 26 February 2002 (2002-02-26) claims; examples	1,2,5-8, 12,13, 22,23, 30-33, 37,38

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01149

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; May 2002 (2002-05) KRYLOV I A ET AL: "'Gastroprotective effect of lycopene in acute gastritis induced by hydrocortisone!" Database accession no. NLM12227088 XP002239844 abstract & EKSPERIMENTAL'NAIA I KLINICHESKAIA FARMAKOLOGIIA. RUSSIA 2002 MAY-JUN, vol. 65, no. 3, May 2002 (2002-05), pages 19-21, ISSN: 0869-2092 -----	1,6,10, 30,31,35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/01149

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 30-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 47
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 47

Present claims 1-7,12-32,37-47 relate to an extremely large number of possible diseases. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the diseases claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the diseases listed in claims 8-11 and in the examples of the application.

Present claim 47 relate to an extremely large number of possible compositions and diseases. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. This claim has not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/01149

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0126668	A	19-04-2001	AU	1135701 A	23-04-2001
			WO	0126668 A1	19-04-2001
WO 0205827	A	24-01-2002	AU	7646201 A	30-01-2002
			WO	0205827 A2	24-01-2002
WO 0189542	A	29-11-2001	WO	0189542 A2	29-11-2001
			US	2002012715 A1	31-01-2002
US 6103756	A	15-08-2000	NONE		
WO 9640092	A	19-12-1996	AU	719671 B2	18-05-2000
			AU	5907896 A	30-12-1996
			CA	2224217 A1	19-12-1996
			EP	0831797 A1	01-04-1998
			WO	9640092 A1	19-12-1996
			GB	2301775 A ,B	18-12-1996
			NZ	309130 A	29-06-2001
			US	6218436 B1	17-04-2001
			US	2001009926 A1	26-07-2001
US 6350776	B1	26-02-2002	NONE		